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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/620,840	07/21/2000	Lance E. Steward	D-2885	4487

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EXAMINER
HAYES, ROBERT CLINTON

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/31/2002

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/620,840	Steward et al
Examiner	**Art Unit**
Robert C. Hayes, Ph.D.	1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 16, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above, claim(s) *2-5 and 12-25* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 6-11, and 26-31* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *1-31* are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *2,4,15*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group I (as it relates to the serotype A species election; claims 1, 6-11 & 26-31) in Paper No. 16 is acknowledged. The traversal is on the ground(s) that the "since all the botulinum toxins are believed to have similar mechanisms of action a single search should suffice" . This is not found persuasive because each of the botulinum toxins are structurally and physically unique as illustrated by their unique amino acid sequences, in which the inventions are further directed to modifications of specific neurotoxins that interact with different proteins; and for the reasons made of record in Paper No: 14. Note that because serotype A "includes a leucine-based motif", claims 2-5 are not an elected invention.

The requirement is still deemed proper and is therefore made FINAL.

Claims 2-5 & 12-25 (i.e., "not... serotype A") are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 14.

Claim Rejections - 35 U.S.C. § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6-11 & 26-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification describes the existence of Clostridium botulinum neurotoxin serotypes A-G, and the mode of action of BoNT/A (e.g., pgs. 2-5 of the specification). No other "neurotoxin" molecules are described within the instant specification. No generic neurotoxin, or modification thereof, is described within the instant specification. Moreover, not even a single modified BoNT/A neurotoxin molecule is structurally described that meets the limitations of that claimed. In contrast, the specification fails to describe what amino acids exactly comprise "structural modifications" with any assayable function, and fails to describe any different species of neurotoxin molecules (i.e., non-BoNT neurotoxins). For example, although pages 34-36 allege prophetic "biological persistences", not a single critical amino acid sequence change in a single neurotoxin molecule that meets a definable "biological persistence" is described. Therefore, one skilled in the art cannot reasonably visualize or predict what critical amino acid residues would structurally characterize the genus of "modified neurotoxin" molecules claimed, or recombinant molecules encoding such, because it is unknown and not described what structurally constitutes any specific modified neurotoxin-like protein from any different species, which are further not described, nor what constitutes any functional modified "regions" thereof when none are specifically described, nor what constitutes a single modified neurotoxin molecule

that meets that limitations of that currently claimed; thereby, not meeting the written description requirement under 35 U.S.C. 112, first paragraph because the claims currently merely constitute an invitation for others to discover their invention.

Applicant is directed toward the Revised Interim Utility and Written Description Guidelines, Federal Register, Vol.64, No.244, pages 71427-71440, Tuesday December 21, 1999.

3. Claims 1, 6-11 & 26-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for specific modified BoNT/A neurotoxin proteins with a definable sequence change and a definable and assayable function, does not reasonably provide enablement for any uncharacterized "structural modification" with no assayable and recited function. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The recitation of "a neurotoxin including a structural modification" as defined on page 15 of the specification encompasses any putative modification, mutation, truncation, substitution, addition and/or deletion within any putative neurotoxin-related protein. However, the inclusion of any biologically functional equivalent or undefinable "structural modification" within any neurotoxin molecule sets forth no structural and little functional characteristics. In contrast, the specification does not teach what amino acids are critical to impart any definable "biological persistence" that can reasonably be reduced or enhanced. Therefore, because the claims

encompass random mutations/modifications of different molecules, and because the specification fails to disclose what residues can be altered and still maintain the desired functional activity of the instant invention, the resultant random mutations/modifications to the claimed neurotoxins would be predicted by the skilled artisan to result in inactive proteins. For example, Rudinger teaches that "it is impossible to attach a unique significance to any residue in a sequence. A given amino acid will not by any means have the same significance in different peptide sequences, or even in different positions of the same sequence" (see page 3). Rudinger further states on page 6 that "the significance of particular amino acid sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study". Therefore, the lack of guidance provided in the specification as to what alterations can be tolerated to maintain an active modified neurotoxin molecule, or what constitutes an assayable "biological persistence" that can reasonably be reduced or enhanced, would prevent the skilled artisan from determining whether any modified neurotoxin could be made that retains the desired function of the instant invention, without requiring undue experimentation to determine otherwise.

4. Claims 1, 6-11 & 26-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite and incomplete for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is ambiguous what metes and bounds exactly constitutes a "modified" neurotoxin, in that no "structural modifications" are recited in the claims for determining what constitutes "structurally different", or for determining when such modifications are "effective to alter [some undefined] biological persistence/ persistence enhancing component", or for determining how such can alternatively be "reduced relative to...." (i.e., as it relates to claim 8) when nothing is specifically recited in the claims for comparison with this otherwise relative term.

It is confusing how a "leucine-based motif" cannot include "one or more amino acids" when leucine itself is "one... amino acid" residues, by definition (i.e., as it relates to claims 7 & 27).

5. Claims 10-11 & 26-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unknown at what point it is envisioned that something is "*substantially* derived", and at what point something is no longer "*substantially* derived"; thereby, making the current claim language ambiguous.

Claim Rejections - 35 U.S.C. § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 6-11 & 26-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Johnson et al. (US Patent 5,939,070; IDS Ref #1).

Johnson et al. teach a modified Clostridial botulinal serotype A neurotoxin that is structurally modified to separate the H and L chains (cols. 8-9; as it relates to claims 1 & 10-11), and therefore, still includes a leucine-based motif (i.e., as it relates to claims 6-7 & 26-27) as well as a first, second and third region as recited in claim 10. Because of this structural chain separation modification, the biological persistence/biological half life of the modified neurotoxin is reasonably reduced; absent evidence to the contrary (e.g. see pg. 13 of the specification; as it relates to claims 8-9 & 29). In the Clostridial neurotoxin was isolated from a naturally existing Clostridial neurotoxin (e.g., col. 7), the limitations of claim 31 are met. In that columns 11-14 teach recombinant production of this neurotoxin and individual domains thereof, the limitations of claim 30 are also anticipated.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (703) 305-3132. The examiner can normally be reached on Monday through Thursday, and alternate Fridays, from 8:30 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert C. Hayes, Ph.D.
December 18, 2002

GARY KUNZ
SUPERVISORY PATENT EXAMINER
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